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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,306	06/05/2002	Antonino Cattaneo	6596	9842

7590 11/29/2005

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,306	CATTANEO ET AL	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 10/11/05.

Claims 2, 10, and 20-37 were canceled as requested.

Claims 1, 3-9, and 11-19 remain pending and are under consideration in this Office Action.

Information Disclosure Statement

An information disclosure statement was received and entered on 10/11/05, correcting the deficiencies of the information disclosure statement of 2/11/02. The references were considered.

Priority

This Application is the national phase of PCT/IT00/00321, filed in English on 7/28/00. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. These include MI99A001783, filed 8/6/99 and RMA000306 filed 6/5/2000. These documents are in the Italian language. Due to the availability of intervening art, a translation of each priority document was required in the previous action, as per 35 USC 365(c).

Applicant asserts at page 5 of the response, that a translation of RMA000306 is included in the submission of 10/11/05. The examiner found no document identified as RMA000306, but did find an unlabeled specification and claims in which the pages of the specification were misnumbered. For example, the 7th and 9th pages are not

numbered, and after the ninth page, the remaining pages are numbered 2-26. So, there specification consists of pages 1-6, unnumbered page, 8, unnumbered page, and 2-26. As a result, substantial doubt remains as to whether or not this document is a translation of RMA000306.

Rule 51*bis* of the Patent Cooperation treaty indicates that the national law applicable by a designated Office may, in accordance with Article 27(2)(ii), require that the translation of the international application furnished by the applicant be:

(i) verified by the applicant or the person having translated the international application in a statement to the effect that, to the best of his knowledge, the translation is complete and faithful;

(ii) certified by a public authority or sworn translator, but only where the designated Office may reasonably doubt the accuracy of the translation.

Due to the ambiguities discussed above, the Office requires, consistent with 37 CFR 1.55, that conditions (i) and (ii) above must be met with regard to RMA000306. The Office requires that condition (i) must be met with regard to MI99A001783.

Specification/Drawings

The specification stands objected to because it contains two copies of page 25.

The brief description of Fig. 1 stands objected to because, although panels A-E are described, panel F is not.

The brief description of Fig. 16 stands objected to because, although panels A, B, and D-F are described, panel C is not.

Appropriate correction is required.

Figure 4 stands objected to because although the brief description mentions panels A and B, the drawing is not labeled accordingly.

Figure 5(c) and Figure 6(c) stand objected to because they are in the Italian language.

Fig. 27 stands objected to because the photomicrographs are inverted relative to the Figure label. Note the inverted A and B in the lower left hand corners of each photo.

Appropriate correction is required.

Applicant's response indicating that the drawings and specification will be corrected after allowance is noted. Applicant is reminded that, to be fully responsive, a response to an action in which the drawings were objected to must include corrected drawings. See 37 CFR 1.85(c) and 37 CFR1.121(d). Objections to the drawings will not be held in abeyance. Drawing corrections should be made promptly before allowance of the application in order to avoid delays in issuance of the application as a patent or a reduction to any term adjustment. See 37 CFR 1.704(c)(10).

Claim Objections

Applicant's amendments were sufficient to overcome the previous objections to claims 1, 4-9, 12, and 19.

Claim 1 is objected to because it refers to "anti-NGH (Nerve Growth Factor)". In light of the specification as filed and instant claims 11 and 14, "NGH" should be deleted

and replaced with --NGF--. Claim 1 is also ungrammatical. Deletion of "a" immediately before "human" is suggested.

Claim 12 is objected to because it was amended by deletion of the word "the" immediately preceding "adult", but its status is identified as "(Original)" instead of "(Currently Amended)", and it is not properly marked up to indicate deletion of "the". Applicant is reminded that 37 CFR 1.121 sets for the proper manner of making amendments to the claims, and requires the use of the proper status identifiers, and that the claims be marked up to show amendments. Failure to comply can result in issuance of a Notice of Non-responsive Amendment.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 43, line 4 discloses an oligonucleotide 9 nucleotides in length that is not accompanied by a SEQ ID NO.** Applicant submitted on 8/11/05 a CRF and paper copy a Sequence Listing, but these documents

contained errors as explained in the attached RAW SEQUENCE LISTING ERROR REPORT. Applicant must correct the error(s) and provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Note that Applicant must also amend the specification to identify the sequence at page 43, line 4 by its SEQ ID NO.

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Rejections Withdrawn

The rejection of claims 1-3, 17, and 18 under 35 U.S.C. 102(b) as being anticipated by Piccioli et al (Neuron 15: 373-384, 1995) is withdrawn in view of Applicant's amendment requiring an animal transgenic for an anti-NGF antibody.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-9, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-9 are indefinite because they recite "the tau protein" without antecedent basis. Deletion of 'the' is suggested.

Claim 9 is indefinite because it recites "the beta amyloid protein deposition in the back or lower limb skeletal muscles" without antecedent basis. Claim 9 also recites "said skeletal muscles" without proper antecedent basis. There are two antecedents for "said skeletal muscles". Table 1 refers to "skeletal muscles" generally at page 10, and claim 9 also recites lower limb skeletal muscles. It is unclear whether "said skeletal muscles" is limited to lower limb skeletal muscles, or whether it includes all skeletal muscles.

Claims 14 is indefinite because it recites "the monoclonal anti-NGF alphaD11 antibody" without proper antecedent basis. It is clear from the disclosure and claims that chimeric and non-chimeric versions of monoclonal anti-NGF alphaD11 antibodies exist. It is unclear to which of these versions the claim refers.

Response to Arguments

Applicant's arguments filed 8/11/05 have been fully considered but they are not persuasive.

Applicant asserts at page 5 of the response that the claims were amended to obviate the rejections. This is unpersuasive. None of the rejections was addressed by any amendment. Each claim continues to recite the same limitations without proper antecedent basis as stated in the previous action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1, 3-9, and 11-19 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly directed to any non-human animal transgenic for an anti-Nerve Growth Factor antibody and having a phenotype "reminiscent of a human neurodegenerative syndromes, muscular atrophy or dystrophy, or immune disorders". Dependent claims add various limitations regarding phenotypic characteristics, identity of transgene, and species of animal. Claim 3 requires that the animal "recapitulates the

features of the human Alzheimer Disease (AD)." In view of the use of the phrase "the features of", this claim has been interpreted to require recapitulation of *each and every* feature of human AD.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by complete structure. It is not realistic to expect that the "complete structure" of a mouse, or any other animal could be described. Therefore the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described. In this case, the specification discloses a transgenic mouse that expresses an antibody against nerve growth factor (NGF). The mouse exhibits a variety of phenotypic characteristics affecting neural and muscular physiology. The specification does not disclose any other animal exhibiting symptoms reminiscent of any human neurodegenerative syndrome, muscular atrophy or dystrophy, or immune disorder. The specification does not disclose any mouse, or other animal exhibiting symptoms reminiscent of a representative number of human neurodegenerative syndromes, muscular atrophy or dystrophy, or immune disorders. For example, such symptoms would include demyelination of motor neurons in multiple sclerosis, inflammation of joints in rheumatoid arthritis (an immune disorder), lack of control over blood glucose levels in autoimmune diabetes, absence of dystrophin in muscular dystrophy, and countless other symptoms of other neurological, muscular, and immune diseases. Further, the specification discloses no mouse that

recapitulates each and every feature of human AD, such as e.g. the gradual loss of speech.

Next, it is to be determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. However, it is not possible to adequately describe the genus of claimed animals because the effects of expression of a heterologous gene can not be predicted. Without evidence to the contrary, transgene expression, or inhibition of gene expression, in different species of transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The specification has not clearly demonstrated or described a method to determine the empirical nature of genetics as it varies among species, in particular the ability of describing an animal resulting from the random insertion of a transgenic construct.

The Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov), state that in an unpredictable art adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. It follows that the disclosure of a single transgenic mouse expressing an anti-NGF antibody and having neuromuscular defects would not convey to one of skill in the art that Applicant was in

possession of the claimed genus, particularly transgenic animals of other species, at the time of the invention.

New Matter

Claims 1, 3-9, and 11-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is broadly directed to any non-human animal transgenic for an anti-Nerve Growth Factor antibody and having a phenotype "reminiscent of a human neurodegenerative syndromes, muscular atrophy or dystrophy, or immune disorders". Dependent claims add various limitations regarding phenotypic characteristics, identity of transgene, and species of animal. Claim 3 requires that the animal "recapitulates the features of the human Alzheimer Disease (AD)." In view of the use of the phrase "the features of", this claim has been interpreted to require recapitulation of *each and every* feature of human AD. The specification as filed does not disclose or contemplate a transgenic animal expressing each an every feature of human AD, so claim 3, as well as its dependents, introduces new matter into the claims. Also, because claim 3 depends from claim 1, claim 1 and its dependents also contain new matter. Deletion of the word "the" immediately before "features" in claim 3 is suggested.

Response to Arguments

Applicant's arguments filed 8/11/05 have been fully considered but they are not persuasive.

Applicant asserts at page 5 of the response that the claims were amended "to obviate" the rejections. No other evidence, reasoning, or logic is given. This is unpersuasive because none of the specific grounds of the rejection were addressed. The rejection is maintained for the reasons set forth above.

Scope of Enablement

Claims 1, 3-9, and 11-19 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse that expresses transgenes encoding the heavy and light chains of an anti-NGF antibody, wherein the mouse has one or more of the following phenotypic characteristics: deposition in the central nervous system of plaques of amyloid precursor protein or beta amyloid protein, hyperphosphorylation of tau protein, neurofibrillary tangles, cortical atrophy, hippocampal atrophy, cerebral ventricle dilation, reduced number of forebrain cholinergic neurons, glial activation, skeletal muscle atrophy, amyloid precursor protein deposits in skeletal muscles, skeletal muscle inflammation, skeletal muscle vacuolization, and a spatial learning deficit, does not reasonably provide enablement for animals other than mice that are transgenic for an antibody and have a phenotype reminiscent of any other human pathology, or for animals that do not express an entire antibody. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 1 is broadly directed to any non-human animal transgenic for an anti-Nerve Growth Factor antibody and having a phenotype "reminiscent of a human neurodegenerative syndromes [sic], muscular atrophy or dystrophy, or immune disorders [sic]. Dependent claims add various limitations regarding phenotypic characteristics, identity of transgene, and species of animal.

The specification discloses a transgenic mouse that expresses heavy and light chains of an antibody against nerve growth factor (NGF). The mouse exhibits a variety of phenotypic characteristics affecting neural and muscular physiology. The specification does not disclose any other animal exhibiting symptoms reminiscent of any human neurodegenerative syndrome, muscular atrophy or dystrophy, or immune disorder. The specification does not disclose any mouse, or other animal exhibiting symptoms reminiscent of a representative number of human neurodegenerative syndromes, muscular atrophy or dystrophy, or immune disorders. For example, such symptoms would include demyelination of motor neurons in multiple sclerosis, inflammation of joints in the immune disorder rheumatoid arthritis, lack of control over blood glucose levels in autoimmune diabetes, absence of dystrophin in muscular dystrophy, and countless other symptoms of other neurological, muscular, and immune diseases. Further, the specification discloses no mouse that recapitulates each and every feature of human AD, such as e.g. the gradual loss of speech. The specification

discloses transgenic mice that express only the heavy or the light chain of the NGF antibody, but discloses no phenotypic characteristics of these mice.

The prior art taught that the production of transgenic animals with desired characteristics is highly unpredictable. The instant invention relies upon expression of an antibody against an endogenous protein e.g. NGF, to approximate the effect of eliminating the expression of that protein. As such, the instant invention is similar to a "knock out" transgenic animal in which a gene of interest has been disrupted. However, at the time of the invention, the phenotype of mice in which expression of targeted genes is reduced was not considered to be predictable. This is apparent from numerous reports. For example, Kappel et al (Curr. Opin. Biol. 3: 548-553, 1992) teach that knock outs of beta2 microglobulin, interleukin 2, interleukin 4, and CD38 were expected to cause severe immuno-incompetence, but this phenotype was not observed in the actual animals. Furthermore, although early developmental lethality was expected for knockouts of src, homozygous src -/- null animals can survive for at least 5 months, and no detrimental effects were observed in the tissues where src expression is highest. Kappel teaches that this unpredictability may be due to developmental plasticity in an organism, otherwise described as the ability of an animal to compensate for one defect through the use of alternative genes or pathways. See paragraph bridging pages 549 and 550, and first three paragraphs on page 550. Melton (BioEssays 16(9): 633-638, 9/1994) summarizes the use of knockout mice to dissect the genetic organization of muscular development. Contrary to expectations, it was found that mice comprising myoD knockouts possessed muscle and developed normally.

Furthermore, myoD null mice had unexpected changes in the expression of myf-5, and myf-5 null mice had changes in the expression of myoD. See last paragraph on page 635 and first paragraph on page 636. Moreadith (J Mol. Med. 75:208-216, 3/1997) teaches that with respect to ideas of gene function, "in many instances [knockouts] have changed the prevailing notions. For example, gene targeting at the endothelin loci subsequently led to the creation of mice with Hirschsprung's disease (aganglionic mega colon) instead of the anticipated phenotype (abnormal control of blood pressure). Indeed if one had even predicted that these mice would survive the absence of a cellular gene that is so widely expressed, one might have been in the minority!" Moreadith goes on to discuss the effects of knocking out the HPRT gene in mice in order to generate a model of Lesch-Nyhan syndrome, noting that the resulting mice had no readily apparent neurological defect. See page 210, column 2, lines 28-34. These teachings, taken together, illustrate the unpredictable nature of knockout mouse phenotypes, and suggest that this is due to the fact that gene interactions are generally poorly understood, as are the potential compensatory actions which are available to the subject animals.

With regard to the scope of transgenic animals embraced by the claims, compared with that exemplified in the specification, the level of skill in the transgenic art is such that one cannot predict whether a transgenic phenotype obtained in a mouse will also be obtained in another animal, even if that animal carries a similar transgene construct. Mullins et al (J. Clin. Invest. (1996) 98(11), Supplement S37-S40) taught that position effects can cause loss of cell specificity of expression, overexpression, or

silencing of the transgene, and that a given construct may react very differently from one animal to another. See page S37, lines 7-12, and page S39, first sentence of first paragraph. Furthermore, Ebert et al (Mol. Endocrinol. 2(3) : 277-283, 1988) disclosed the production of transgenic mice expressing human somatotropin regulated by the mouse metallothionein promoter at levels sufficient to cause an increase in growth; however, expression of the same transgene in pigs did not produce pigs exhibiting the same phenotypic result (page 277, Introduction, column 2). Also, Hammer et al (J. Anim. Sci. 63 : 269-278, 1986), disclosed the production of transgenic mice, sheep and pigs expressing human growth hormone, however only mice exhibited an increase in growth due to the expression of the transgene (pages 276-277, Subsection: (Effect of Foreign GH on Growth). The inability to extrapolate phenotypes observed in mice to other animals is the result of a variety of unpredictable factors including, for example, the site of integration and methylation-inactivation of the transgene. See Kappel et al (1992), right column of page 549. Also, Wall (Theriogenology 45: 57-68, 1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). The nature of the chromatin at the site of insertion can control the expression of the transgene with respect to developmental timing, tissue specificity, and frequency of transcription initiation. These position effects vary with the site of integration, which is totally unpredictable.

With respect to the breadth disease phenotypes embraced by the claims, the specification provides no correlation between anti-NGF antibody expression and the various neurological and muscular defects listed in the statement of the rejection. However, as noted above, the claims clearly embrace other phenotypes that are unrelated to the anti-NGF phenotype, such as diabetes, demyelination in multiple sclerosis, loss of dystrophin in muscular dystrophy, and inflammation in arthritis. The specification as filed simply does not teach one of skill in the art how to produce these phenotypes by expressing anti-NGF antibodies in a mouse or any other organism.

In view of the art-recognized unpredictability of transgenic animal phenotypes, the unpredictability associated with transgene expression, the inability to predictably obtain similar phenotypes in different species, the failure of the specification to provide the guidance that is missing from the prior art in those regards, as well as the failure of the specification to provide any correlation between anti-NGF antibodies and a wide variety of human neurodegenerative syndromes, muscular atrophy or dystrophy phenotypes, and immune disorders, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 8/11/05 have been fully considered but they are not persuasive.

Applicant asserts at page 5 of the response that the claims were amended "to obviate" the rejections. No other evidence, reasoning or logic is given. This is

unpersuasive because none of the specific grounds of the rejection were addressed. The rejection is maintained for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-9, and 11-19 stand rejected under 35 U.S.C. 102(a) as being anticipated by Ruberti et al (J. Neurosci 20(7): 2589-2601, 4/2000), as evidenced by Ruberti et al (Cell. Mol. Endocrinol. 13(5): 559-568, 1993).

Ruberti taught a B6SJL mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. See abstract, and paragraph bridging pages 2589 and 2590. Evidence that the antibody is a humanized chimeric antibody is found in the abstract of Ruberti et al (1993), referred to by Ruberti (2000) at the first sentence of paragraph bridging pages 2589 and 2590. Phenotypic characteristics of the mice included expression of the antibody primarily in adulthood, reduced cholinergic neurons in adults but not early postnatal mice, as well as atrophy of skeletal muscles in adult but not post-natal mice. See abstract. The limitations of claim 9 are considered to be met inasmuch as the muscular atrophy occurred at the same time as the reduction in cholinergic neurons, i.e. in the adult. Claim limitations not specifically disclosed by

Ruberti are considered to be inherent in the mouse of Ruberti because its genetic structure is indistinguishable from that of the claimed mouse, and the phenotypic characteristics necessarily flow from the genetic structure. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

It is noted that the three inventors of the instant application are authors of the Ruberti et al reference. However, the reference also cites six other authors not currently listed as inventors. As such, the invention was known or used by another in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. See MPEP 2132 which states:

> The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use.

Thus Ruberti anticipates the claims.

Claims 1, 3-9, and 11-19 stand rejected under 35 U.S.C. 102(a) as being anticipated by Capsoni et al (J. Neuroscience Res. 59:553-560, 2/2000).

Capsoni taught a B6SJL mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. See abstract, paragraph bridging pages 553 and 554, and first full paragraph on page 554. The phenotype of the animals includes muscular atrophy, myositis, shrinkage of cholinergic neurons, and reduced clustering of acetylcholine receptors. See abstract; sentence bridging pages 555 and 556; paragraph bridging columns 1 and 2 on page 559, and first full paragraph of column 2 on page 559. This is considered to be reminiscent of human pathologies such as Alzheimer's and muscular dystrophy. Claim limitations not specifically disclosed by Capsoni are considered to be inherent in the mouse of Capsoni because its genetic structure is indistinguishable from that of the claimed mouse, and the phenotypic characteristics necessarily flow from the genetic structure. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430,

433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

It is noted that the three inventors of the instant application are authors of the Capsoni et al reference. However, the reference also cites a fourth author who is not currently listed as an inventor. As such, the invention was known or used by another in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent. See MPEP 2132 which states:

> The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C. 102(a) including publications as well as public knowledge and use.

Thus Capsoni anticipates the claims.

Claims 1, 3-9, and 11-19 stand rejected under 35 U.S.C. 102(a) as being anticipated by Capsoni et al (Proc. Nat. Acad. Sci. USA 97(12): 626-6830, 2000) as evidenced by Ruberti et al (J. Neurosci 20(7): 2589-2601, 4/2000).

Capsoni taught a mouse transgenic for a chimeric, humanized alphaD11 monoclonal antibody against NGF. It is clear that the mouse is a B6SJL mouse because Capsoni refers to Ruberti (2000) for details on construction of the mouse, and Ruberti discloses a B6SJL mouse that expresses the anti-NGF antibody. The mouse has a phenotype consistent with Alzheimer-like neurodegeneration, including amyloid plaques, hyperphosphorylated tau, neurofibrillary tangles in cortical and hippocampal neurons, ventricle dilation, cortical and hippocampal atrophy, cholinergic deficit in the

forebrain , dystrophic neurites, and spatial memory and object recognition impairments. See entire document.

Claims 1, 3-9, and 11-18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cattaneo et al (Society for Neuroscience Abstracts 22 (1-3): 753, 1996).

Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The mice show a 30% reduction in neurons of the superior cervical ganglia. This phenotypic characteristic is considered to be reminiscent of neurodegenerative diseases. Claim limitations not specifically disclosed by Cattaneo are considered to be inherent in the mouse of Cattaneo because its genetic structure is indistinguishable from that of the claimed mouse, and the phenotypic characteristics necessarily flow from the genetic structure. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430,

433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Response to Arguments

Applicant's arguments filed 8/11/05 have been fully considered but they are not persuasive.

Applicant asserts at page 6 of the response that the Ruberti (2000), and Capsoni (2000) references are not proper references under 35 USC 102 because they are antedated by the foreign priority document MI99A001783. This is unpersuasive because this document is in the Italian language, and Applicant has not yet complied with 35 USC 365(c) by filing a translation into English. As a result, the cited references are proper references under 35 USC 102(a).

Applicant addresses the Cattanao (1996) reference at pages 7-10 of the response. Applicant argues that the mouse of Cattaneo (1996) is not the mouse described in the present application. Briefly, Applicant asserts that the parental strains required to produce the claimed mouse differ in the level of antibody heavy and light chains that they produce. The claimed mouse is allegedly produced by crossing parental lines that produce far more of the heavy and light chains than do the parental strains in the Cattaneo reference, such that the offspring produce far more of the complete antibody. This allegedly results in phenotypic differences detailed at pages 8-10 of the response. Although these arguments are presented with what appear to be supporting experimental data, they are not set forth in a declaration under 37 CFR

1.132, and accordingly they are considered to be arguments of counsel. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, **inoperability of the prior art**, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Because Applicant's arguments are not supported by evidence, they are unpersuasive.

In any case, Applicant's arguments could not overcome the rejection of claims 1 and 11-18 because the 30% reduction in neurons of the superior cervical ganglia reported by Cattaneo is considered to be reminiscent of a human neurodegenerative syndrome to the extent that such a syndrome involves a reduction in neurons, and because Cattaneo taught all of the limitations of claims 11-18. Applicant has provided no evidence or argument to the contrary.

Note that should Applicant submit evidence under 37 CFR 1.132 that proved that the mice of Cattaneo (1996) did not have the claimed phenotypic characteristics, even though they comprised an identical transgene, this would constitute evidence of the unpredictability of the phenotype of the claimed transgenic mice. In particular, since there is no discernable difference in the structure of the mice, and no guidance as to how to reproducibly make the parental mice of the instant invention instead of the parental mice of Cattaneo (1996), it would appear that the parental strains would have

to be deposited under the conditions of 37 C.F.R. 1.801-1.809 in order to enable claims to a mouse made by crossing those specific lines.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cattaneo et al (1996) in view of Hogan et al (In *Manipulating the Mouse Embryo,* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pg 81, 1986).

Cattaneo taught a transgenic mouse comprising a transgene encoding the variable regions of mouse monoclonal antibody against NGF joined to human constant regions, under the control of a CMV early promoter. Antibody was expressed at 50-100 ng/ml in adult mice. The mice show a 30% reduction in neurons of the superior cervical ganglia. This phenotypic characteristic is considered to be reminiscent of human neurodegenerative diseases.

Hogan taught that there was a variety of mouse hybrid zygotes that were suitable for the formation of transgenic mice, including hybrids of C57BL/6J and SJL mice, i.e. B6SJL zygotes. See page 81.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the B6SJL hybrid zygotes of Hogan to make the transgenic mice of

Cattaneo because Hogan indicated that these zygotes were among several types of zygotes routinely used for the purpose of making transgenic animals. The selection of a particular zygote were among several suitable types is merely a matter of design choice and, absent case specific indications to the contrary, the zygotes available for use can be viewed as art-recognized equivalents.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 8/11/05 have been fully considered but they are not persuasive.

Applicant addresses the rejection at pages 10-12 of the response. Applicant states that Cattaneo (1996) suggested that crossing two particular lines of mice would result in a mice having circulating anti-NGF antibodies at levels of 50-100 ng/ml, and that Hogan taught a general procedure for how to manipulate a mouse embryo. Absent any further logical steps, Applicant then concludes that a person skilled in the art would not have predicted from Cattaneo and Hogan that one could obtain transgenic mice having a list of 14 phenotypic characteristics that are not that not recited as limitations in the rejected claims. The argument is unpersuasive because Applicant argued limitations that are not in the claims, and Applicant failed to address the stated reasons for combining the references, or provide any basis in logic or reason to show that the references were not combinable. Note that the arguments against the Cattaneo reference as used under the 35 USC 102 rejection, briefly reiterated at page 12 of the

response, were unpersuasive for the reasons set forth above, and are not persuasive regarding the 103 rejection either.

For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.